Efficacy and Safety of Blood Derivative Therapy for Patients with COVID-19: A Systematic Review and Meta-Analysis

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Abstract

Background: The outbreak of COVID-19 has resulted in more than 200 million infections and 4 million deaths. The blood derivative therapy represented by intravenous immunoglobulin (IVIG) and convalescent plasma (CP) therapy may be the promising therapeutics for COVID-19. ***Methods:*** A systematic article search was performed for eligible studies published up to August 3, 2021, through the PubMed, Embase, Cochrane Library. The included articles were screened by using rigorous inclusion and exclusion criteria. All analyses were conducted using Review Manager 5.4. Quality of studies and risk of bias were evaluated. ***Results:*** A total of 5 IVIG therapy and 13 CP therapy randomized controlled trials were included with a sample size of 13,696 subjects diagnosed with COVID-19. IVIG could reduce the mortality compared with the control group (RR 0.65, 95% CI: 0.46–0.93, p = 0.02). The use of CP did not effectively reduce the mortality (RR 0.97, 95% CI: 0.91–1.03, p = 0.38), the length of hospital stay (MD −0.47, 95% CI: −4.13 to 3.20, p = 0.80), and the mechanical ventilation use (RR = 0.98, 95% CI: 0.89–1.07, p = 0.62) of the patients with COVID-19. Treatment with IVIG or CP was not significantly associated with an increase in reported adverse events (RR 1.07, 95% CI: 0.94–1.22, p = 0.28). ***Conclusions:*** Treatment with IVIG could be effective and safe to improve survival for patients with COVID-19. But the benefit of CP in the treatment of COVID-19 is limited. The certainty of the evidence was moderate for all outcomes.

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Introduction

Since the outbreak of COVID-19 emerged in Wuhan, China, in December 2019, it has been diagnosed in nearly 200 million individuals around the world, of whom around 4 million have died [1]. Many severely affected patients with COVID-19 develop severe acute respiratory illness requiring mechanical ventilation, among whom the case-fatality rate can even reach 40% [2, 3]. This pandemic is not only a great challenge to the health care system but also a serious threat to the life and health of all mankind. Although the COVID-19 vaccine has been successfully developed and mass-produced [4], it is still in short supply due to the large population base. And it was reported that the vaccine did not show 100% efficacy against COVID-19 [5], and the fully vaccinated people might also be reinfected [6]. At present, not only the number of confirmed cases and deaths with COVID-19 are still rising but also SARS-CoV-2 variants have appeared in many parts of the world such as the UK [7] (SARS-CoV-2 variants B.1.1.7), South Africa [8] (B.1.351), and Brazil [9] (P.1). The B.1.617.2 (delta) variant of SARS-CoV-2 has contributed to a surge in cases in India and has
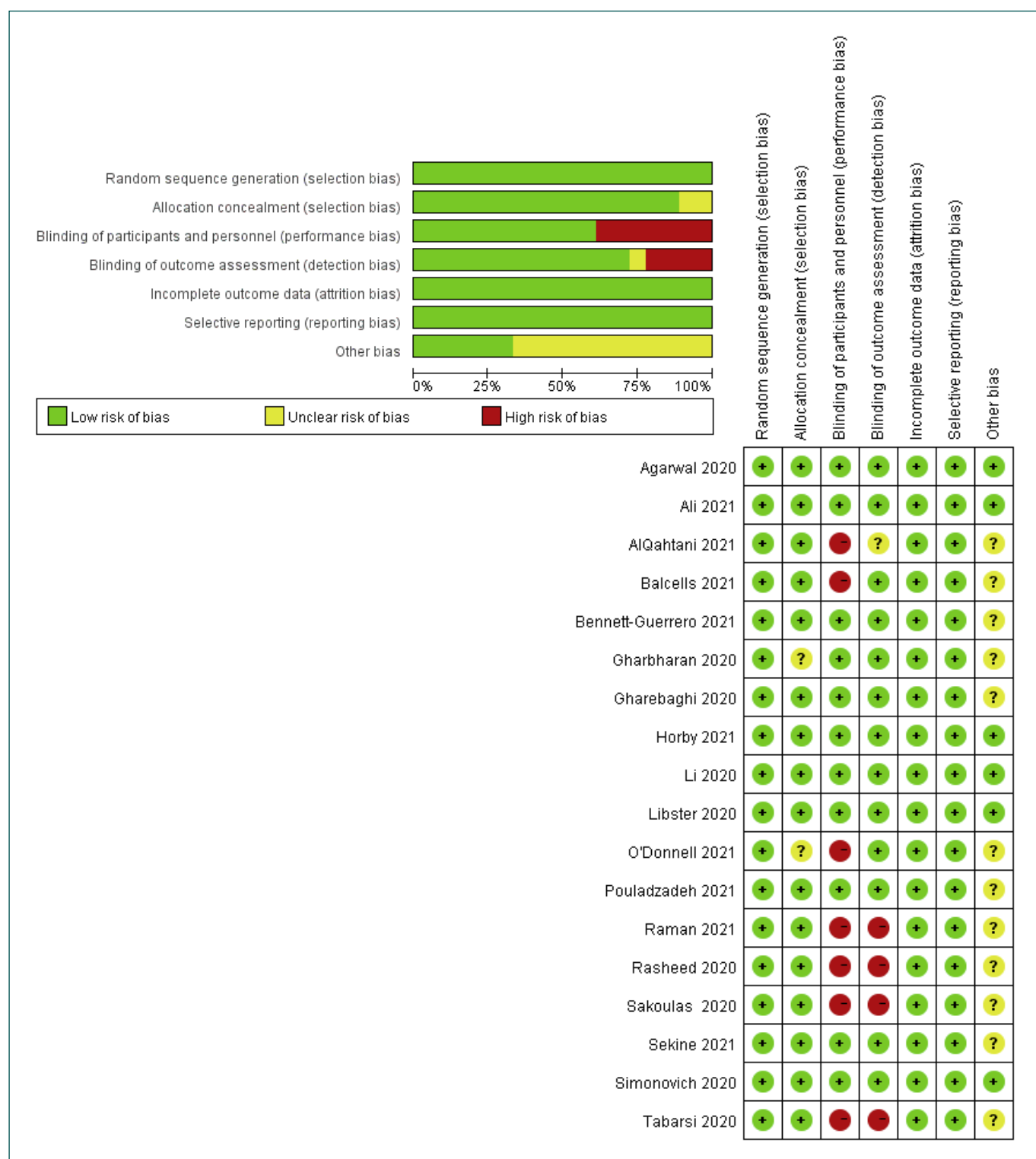
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Fig. 1. Risk of bias graph and summary.

now been detected across the world. These variants often show stronger infectivity and immune escape ability [10–12]. The second wave of COVID-19 pandemic in India [13] (hundreds of thousands of daily infections) shows that we need to find effective and safe treatments to treat as many infected patients as possible while producing vaccines.

No known treatment showed definitive clinical effects on COVID-19 as the efficacy of antiviral agents [14], glucocorticoids [15], and antibiotics [16] in clinical practice

Fei/Chen/Du/Cao/Li

were controversial. As an ancient disease intervention, blood derivative therapy played a great role in the clinical treatment of many pandemics, including COVID-19. Among all the pharmacological interventions for patients with COVID-19, the blood derivative therapy represented by intravenous immunoglobulin (IVIG) and convalescent plasma (CP) therapy may be the most promising therapeutics due to the efficiency and safety of these two treatments in some clinical trials. IVIG, containing the full range of antibody spectrum, is derived from the plasma of thousands of healthy donors. The use of IVIG for COVID-19 within 14 days of onset was related to the reduction of 28-day mortality in a multicenter retrospective study involving 26 patients in China [17]. CP therapy is the transfusion of blood collected from recovered individuals to infected patients. It has been used for a variety of severe respiratory viral infections such as SARS [18], MERS [19], and Ebola [20] to improve the clinic prognosis of patients. And it was found that CP therapy could have beneficial effects on patient outcomes in an observational clinical study involving 24 patients with COVID-19 [21].

Due to the exigency of the epidemic, it is urgent to know whether blood derivative therapy is effective for patients with COVID-19. There were some systematic reviews of IVIG and CP, but the quality of evidence of researches was low because of the inclusion of nonrandomized controlled trials [22–24]. And the reliable clinical evidence of benefits or harm was limited if only from the previous reviews. Therefore, we systematically retrieved the related studies and conducted this meta-analysis to determine the safety and efficacy of IVIG and CP for COVID-19 and the different treatment effects between these two therapeutics to provide references for treating COVID-19.

Methods

This meta-analysis was performed according to the PRISMA guidelines (online suppl.; for all online suppl. material, see www.karger.com/doi/10.1159/000524125). The review has been registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO/. CRD42021249391).

Design and Search Strategy
The search included articles in English or Chinese language published in the PubMed, Embase, Cochrane Library through August 3, 2021. The search was conducted using the following keywords: COVID-19 or sars-cov-2 infection or novel coronavirus 2019 infection and COVID-19 serotherapy or convalescent plasma or Immunoglobulins, Intravenous or immunoglobulin or IVIG or hyperimmune globulin. The detailed retrieval strategy can be found in the online supplementary. This study was designed and conducted according to the PRISMA reporting guideline. The references to the included articles and reviews were also searched for citations of additional relevant published and unpublished studies.
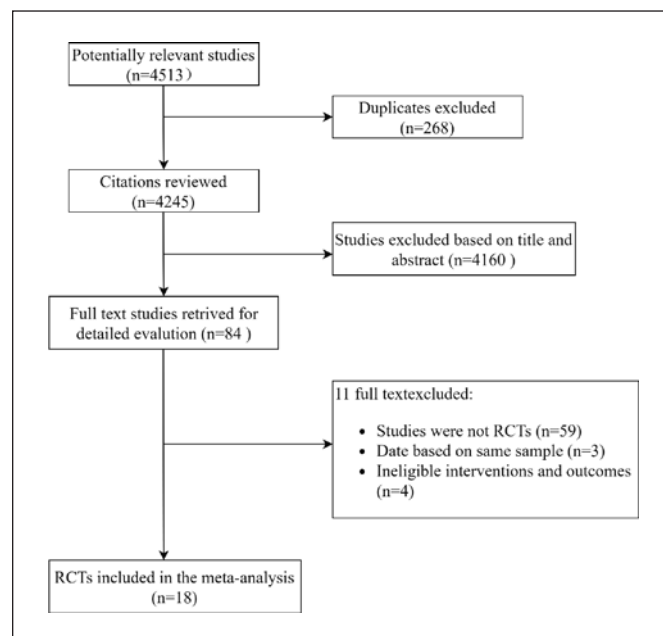

Fig. 2. Study flow diagram.

Criteria for Inclusion and Exclusion
Inclusion criteria for the systematic review were: (1) a randomized controlled study design that did not require mortality data to ascertain outcome; (2) all subjects were diagnosed with COVID-19 regardless of the condition; (3) the experimental group was not given intervention other than blood transfusion with standard of care, and the control group was allocated to receive placebo together with standard of care, or only standard of care. Studies were excluded if (1) study reported insufficient details to derive the outcomes; (2) study had other interventions; (3) full text of the study was not available in the databases; (4) study was written in languages other than English and Chinese.

Study Outcomes
The outcomes of efficacy were all-cause mortality, number of patients requiring mechanical ventilation, length of hospital stay in the treatment group, and standard care groups. The outcomes of safety were the reported adverse events.

Data Extraction
One investigator (Z.F.) performed the literature search and screening, and 2 investigators (Z.C and X.D.) independently performed data extraction. Discrepancies were resolved through discussion between investigators. The extracted data items include: (1) study characteristics: design, location, year of publication; (2) participant characteristics: age, sex, details of the intervention, treatment duration, and all clinical assessment.

Risk of Bias
We scored the studies that met inclusion criteria according to the Cochrane risk of bias tool [14], which evaluates the random sequence generation, allocation concealment, blinding of participants, personal and outcome assessment, incomplete outcome data, selective outcome reporting, and other biases (Fig. 1). The included RCTs were classified as low risk (L), high risk (H), or unclear risk (U) in the above items.

Table 1. Characteristics of RCTs included in this systematic review

Source	Study design	Total, n	Intervention group (1) Number (2) Subject condition (3) Age, mean (SD) (4) Male (%) (5) Treatment	Control group (1) Number (2) Subject condition (3) Year, mean (SD) (4) Male (%) (5) Treatment	Outcomes intervention: control (n)	Dose description	Treatment since symptom onset	Risk of bias
Gharebaghi et al. [25] Iran	RCT, single-center	59	(1) 30 (2) Severe (3) 55.5 (45, 60)[a] (4) 21 (70) (5) IVIG + standard of care	(1) 29 (2) Severe (3) 56 (47, 66)[a] (4) 20 (68.9) (5) Placebo + standard of care	Death number: 6:14 Mechanical ventilation: NR	IVIG 20 g/d for 3 days	48 h	L, L, L, L, U
Tabarsi et al. [26] Iran	RCT, single-center	84	(1) 52 (2) Severe (3) 54.29 (12.85) (4) 40 (76.92) (5) IVIG + standard of care	(1) 32 (2) Severe (3) 52.47 (14.49) (4) 25 (78.12) (5) Standard of care	Death number: 24:14 Mechanical ventilation: 21:10	IVIG 0.4 g/kg/d for 3 days	<7 days	L, L, H, H, L, U
Sakoulas et al. [27] USA	RCT, multiple-center	33	(1) 16 (2) Severe (3) 54 (4) 10 (63) (5) IVIG + standard of care	(1) 17 (2) Severe (3) 54 (4) 10 (59) (5) Standard of care	Death number: 1:3	IVIG 0.5 g/kg/d for 3 days	13.2 (SD 6.6) days	L, L, L, L, L, L
Raman et al. [28] India	RCT, multiple-center	100	(1) 50 (2) Moderate (3) 48.4 (11.6) (4) 14 (28) (5) IVIG + standard of care	(1) 50 (2) Moderate (3) 49 (13.5) (4) 19 (38) (5) Standard of care	Death number: 0:1 Mechanical ventilation: NR	0.4 g/kg for 5 days	NR	L, L, H, H, L, U, U
Ali et al. [29] Pakistan	RCT, single-center	50	(1) 40 (2) Severe-critically (3) 55.9 (1.34) (4) 28 (70) (5) IVIG + standard of care	(1) 10 (2) Severe-critically (3) 59.1 (12.06) (4) 7 (70) (5) Standard of care	Death number: 10:6 Mechanical ventilation: 2:0	Single dose of 0.15/0.20/0.25/0.3 g/kg anti-COVID-19 IVIG	<14 days	L, L, L, L, L, L
Simonovich et al. [30] Argentina	RCT, multiple-center	333	(1) 228 (2) Severe (3) 62.5 (53–72.5)[a] (4) 161 (71) (5) CP + standard of care	(1) 105 (2) Severe (3) 62 (49–71)[a] (4) 64 (61) (5) Placebo + standard of care	Death number: 25:12 Mechanical ventilation: 19:10	Single transfusion of 10–15 mL/kg High titer (>1:800)	Any time	L, L, L, L, L
Agarwal et al. [31] India	RCT, multiple-center	464	(1) 235 (2) Moderate (3) 52 (42–60)[a] (4) 177 (75) (5) CP + standard of care	(1) 229 (2) Moderate (3) 52 (41–60)[a] (4) 177 (77) (5) Standard of care	Death number: 34:31 Mechanical ventilation: 19:19	2 doses of 200 mL CP 24 h apart	Any time	L, L, L, L, L

Table 1 (continued)

Source	Study design	Total, n	Intervention group (1) Number (2) Subject condition (3) Age, mean (SD) (4) Male (%) (5) Treatment	Control group (1) Number (2) Subject condition (3) Year, mean (SD) (4) Male (%) (5) Treatment	Outcomes intervention: control (n)	Dose description	Treatment since symptom onset	Risk of bias
Rasheed et al. [32] Iraq	RCT, single-center	49	(1) 21 (2) Critically-ill (3) 55.66 (17.83) (4) 12 (57.1) (5) CP + standard of care	(1) 28 (2) Critically-ill (3) 47.82 (15.36) (4) NR (5) Standard of care	Death number: 1:8 Mechanical ventilation: 17:16	NR	3 days	L, L, H, H, L, L, U
Libster et al. [33] Argentina	RCT, single-center	160	(1) 80 (2) Mild (3) 76.4 (8.7) (4) 26 (32) (5) CP + standard of care	(1) 80 (2) Mild (3) 77.9 (8.4) (4) 34 (42) (5) Placebo + standard of care	Death number: 2:4 Mechanical ventilation: 3:10	Single transfusion of 250 mL, high titer (>1:1,000)	≤3 days	L, L, L, L, L, L
Li et al. [34] China	RCT, multiple-center	103	(1) 52 (2) Severe-critically (3) 70 (62–80)[a] (4) 27 (52) (5) CP + standard of care	(1) 51 (2) Severe-critically (3) 69 (63–76)[a] (4) 33 (65) (5) Standard of care	Death number: 8:12 Mechanical ventilation: NR	Single transfusion of 4–13 mL/kg	Any time	L, L, L, L, L, L
Gharbharan et al. [35] The Netherlands	RCT, multiple-center	86	(1) 43 (2) NR (3) 61 (56–70)[a] (4) 29 (67) (5) CP + standard of care	(1) 43 (2) NR (3) 63 (55–77)[a] (4) 33 (77) (5) Standard of care	Death number: 6:11 Mechanical ventilation: NR	Single transfusion of 300 mL, low titer (≥1:400)	Any time	L, U, L, L, L, L, U
Horby et al. [36] UK	RCT, multiple-center	11,558	(1) 5,795 (2) Suspected or confirmed (3) 63.5 (14.7) (4) 3,643 (63) (5) CP	(1) 5,763 (2) Suspected or confirmed (3) 63.4 (14.6) (4) 3,787 (66) (5) Standard of care	Death number: 1,399:1,408 Mechanical ventilation: 678:690	Two units (200–350 mL) intravenously	<21 days	L, L, L, L, L, L
AlQahtani et al. [37] Bahrain	RCT, multiple-center	40	(1) 20 (2) Severe and life-threatening (3) 50.7 (12.5) (4) 15 (75) (5) CP	(1) 20 (2) Severe and life-threatening (3) 52.6 (14.9) (4) 17 (85) (5) Standard of care	Death number: 1:2 Mechanical ventilation: 4:6	2 transfusions of 500 mL administered, over 24 h	NA	L, L, H, U, L, L, U
Bennett-Guerrero et al. [38] USA	RCT, single-center	74	(1) 59 (2) Mild and severe (3) 67 (15.8) (4) 36 (61) (5) CP	(1) 15 (2) Mild and severe (3) 64 (17.4) (4) 8 (53.3) (5) Standard plasma	Death number: 16:5 Mechanical ventilation: NR	Two units (480 mL) intravenously	<21 days	L, L, L, L, L, U

Table 1 (continued)

Source	Study design	Total, n	Intervention group (1) Number (2) Subject condition (3) Age, mean (SD) (4) Male (%) (5) Treatment	Control group (1) Number (2) Subject condition (3) Year, mean (SD) (4) Male (%) (5) Treatment	Outcomes intervention: control (n)	Dose description	Treatment since symptom onset	Risk of bias
Pouladzadeh et al. [39] Iran	RCT, single-center	62	(1) 31 (2) Mild and severe (3) 53.5 (10.3) (4) 16 (53.3) (5) CP	(1) 31 (2) Mild and severe (3) 57.2 (17) (4) 17 (56.7) (5) Standard of care	Death number: 3:5 Mechanical ventilation: 3:5	Administration of 500 mL CP intravenously	<7 days	L, L, L, L, L, U
Balcells et al. [40] Chile	RCT, single-center	58	(1) 28 (2) Mild and severe (3) 64.3 (4) 15 (53.6) (5) CP	(1) 30 (2) Mild and severe (3) 67.1 (4) 14 (46.7) (5) Standard of care	Death number: 5:2 Mechanical ventilation: 5:2	2 Transfusions of 200 mL administered, 24 h apart	<7 days	L, L, H, L, L, U
O'Donnell et al. [41] USA and Brazil	RCT, multiple-center	223	(1) 150 (2) Severe-critically (3) 60 (48–71)[a] (4) 96 (64) (5) CP	(1) 73 (2) Severe-critically (3) 63 (49–72)[a] (4) 51 (70) (5) Normal control plasma	Death number: 19:18 Mechanical ventilation: NR	Single transfusion of 200–250 mL. Titer 1:160 (IQR 1:80–1:320)	<14 days	L, U, H, L, L, U
Sekine et al. [42] Brazil	RCT, single-center	160	(1) 80 (2) Severe (3) 59.0 (48.0–68.5) (4) 49 (61.2) (5) CP	(1) 80 (2) Severe (3) 62.0 (49.5–68.0) (4) 44 (55.0) (5) Standard of care	Death number: 16:13 Mechanical ventilation: 12:10	Transfusion of 2 aliquots of 300 mL of CP, 2 days apart	<15 days	L, L, L, L, L, U

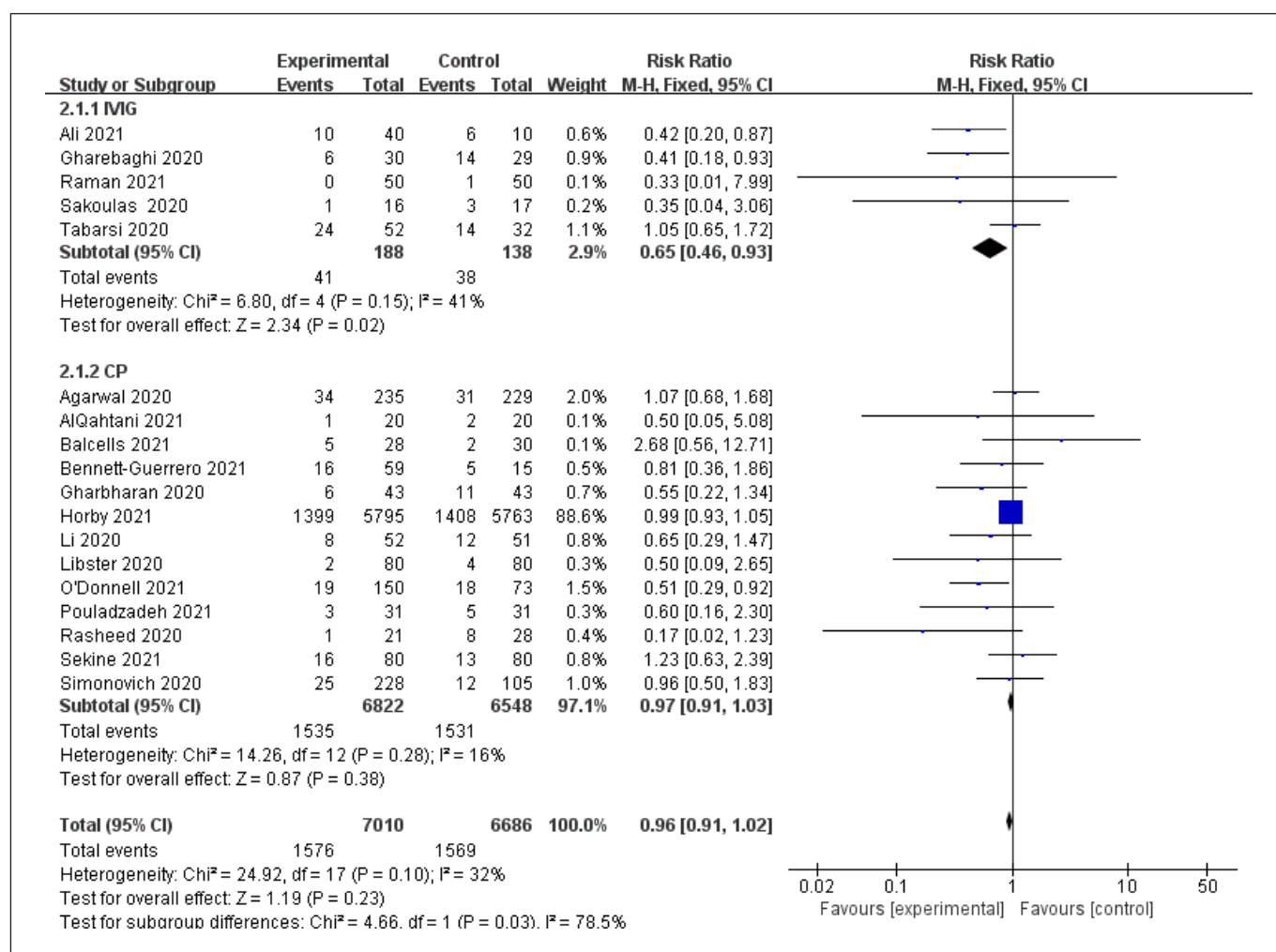NA, not reported. [a] Data are presented using median (IQR).

Fig. 3. Forest plots of all-cause mortality (18 comparisons, *n* = 13,696).

Results

A total of 4,513 references were identified from the databases (Fig. 2). After excluding duplications and screening of titles and abstracts, the full papers of 84 studies were obtained and assessed for eligibility. According to the inclusion criteria, the definitive analysis included 5 IVIG RCTs [25–29] (*n* = 326) and 13 CP RCTs [30–42] (*n* = 13,370). All of 18 trials were fully published in peer-reviewed journals in 2020 and 2021 for individuals with COVID-19 from the USA, India, China, Argentina, Netherlands, Iraq, Pakistan, Brazil, Bahrain, UK, and Iran. Out of the 18 trials, mortality was assessed in all 18 RCTs after randomization. Length of hospital stay was available in 8 RCTs [25–28, 31, 36, 40, 41] (4 IVIG and 4 CP). The need for mechanical ventilation use was reported in 12 RCTs [26, 27, 29–37, 39, 40, 42] (3 IVIG and 9 CP). Reported adverse events were evaluated in patients [27–35, 41, 42] (3 IVIG and 8 CP). Concrete information of included studies were listed in Table 1. All analyses were conduct-

ed using Review Manager 5.4. A random-effects model was used for this meta-analysis when there was no heterogeneity, or else a fixed-effects model would be used. Sensitivity analyses were performed by sequentially removing one study at a time to identify the studies that influenced the results significantly.

Mortality

Whether IVIG and CP can reduce the mortality of CO-VID-19 patients is the most important purpose to do this meta-analysis in the current global context of COVID-19 pandemic. Evidence from 13 RCTs [30–42] (*n* = 13,370) of COVID-19 patients showed inconclusive effects of CP on 28-day mortality (Fig. 3): RR 0.97, 95% CI: 0.91–1.03, *p* = 0.38; heterogeneity χ^2 = 14.26, df = 12, *p* = 0.28, I^2 = 16%. But IVIG did play a great role in reducing the mortality of COVID-19 patients in 5 RCTs [25–29] (*n* = 326) in this meta-analysis (Fig. 3): RR 0.65, 95% CI: 0.46–0.93, *p* = 0.02; heterogeneity χ^2 = 6.8, df = 4, *p* = 0.15, I^2 = 41%.

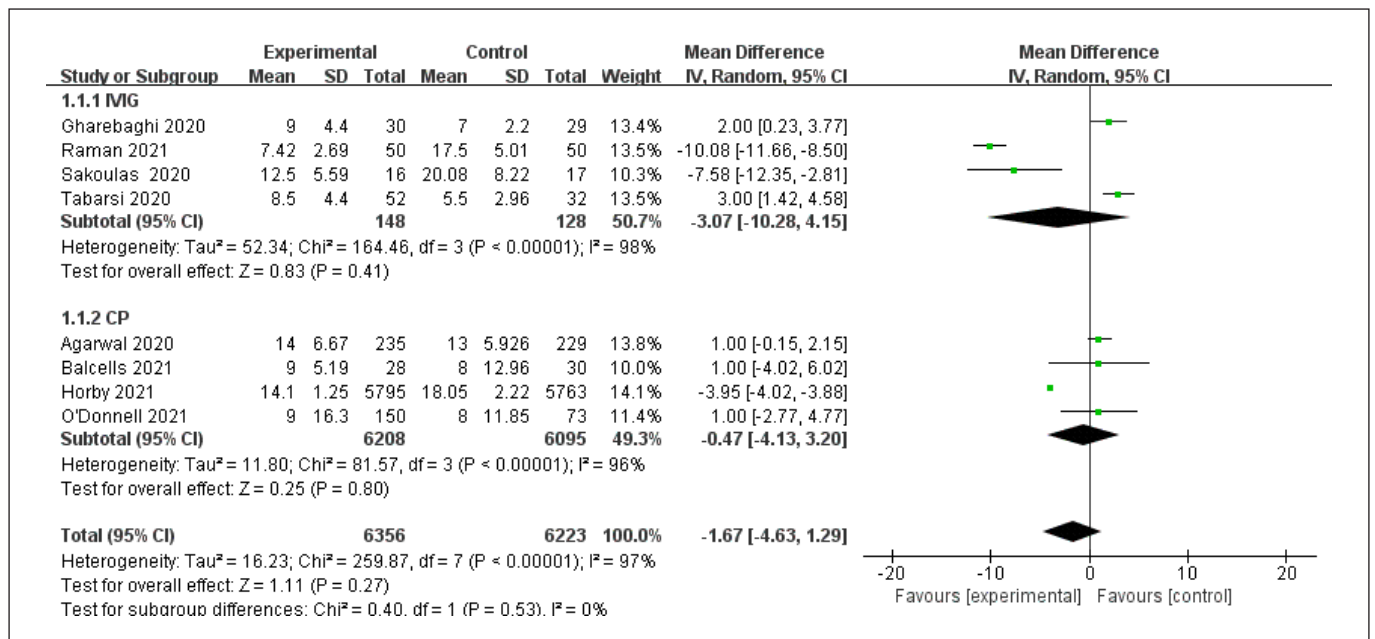| Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
1.1.1 IVIG									
Gharebaghi 2020	9	4.4	30	7	2.2	29	13.4%	2.00 [0.23, 3.77]	
Raman 2021	7.42	2.69	50	17.5	5.01	50	13.5%	-10.08 [-11.66, -8.50]	
Sakoulas 2020	12.5	5.59	16	20.08	8.22	17	10.3%	-7.58 [-12.35, -2.81]	
Tabarsi 2020	8.5	4.4	52	5.5	2.96	32	13.5%	3.00 [1.42, 4.58]	
Subtotal (95% CI)			148			128	50.7%	-3.07 [-10.28, 4.15]	
Heterogeneity: Tau² = 52.34; Chi² = 164.46, df = 3 (P < 0.00001); I² = 98%									
Test for overall effect: Z = 0.83 (P = 0.41)									
1.1.2 CP									
Agarwal 2020	14	6.67	235	13	5.926	229	13.8%	1.00 [-0.15, 2.15]	
Balcells 2021	9	5.19	28	8	12.96	30	10.0%	1.00 [-4.02, 6.02]	
Horby 2021	14.1	1.25	5795	18.05	2.22	5763	14.1%	-3.95 [-4.02, -3.88]	
O'Donnell 2021	9	16.3	150	8	11.85	73	11.4%	1.00 [-2.77, 4.77]	
Subtotal (95% CI)			6208			6095	49.3%	-0.47 [-4.13, 3.20]	
Heterogeneity: Tau² = 11.80; Chi² = 81.57, df = 3 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 0.25 (P = 0.80)									
Total (95% CI)			6356			6223	100.0%	-1.67 [-4.63, 1.29]	
Heterogeneity: Tau² = 16.23; Chi² = 259.87, df = 7 (P < 0.00001); I² = 97%									
Test for overall effect: Z = 1.11 (P = 0.27)									
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%									

Fig. 4. Forest plots of the length of hospital stay (8 comparisons, n = 1,061).

Length of Hospital Stay and Mechanical Ventilation Use

For CP group, 4 RCTs [31, 36, 40, 41] with 785 patients were available for length of hospital stay in this meta-analysis. It showed no significant associations between treatment with CP and reductions in length of hospital stay (Fig. 4): MD −0.47, 95% CI: −4.13 to 3.20, p = 0.80. It was found that IVIG also could not reduce the length of hospital stay in 4 RCTs [25–28] with 276 patients (Fig. 4): MD −3.07, 95% CI: −10.28 to 4.15, p = 0.41; heterogeneity χ^2 = 164.46, df = 3, p < 0.00002, I^2 = 98%. There were no significant differences between the intervention group (CP and IVIG) and the placebo group in the number of patients with mechanical ventilation use (Fig. 5). For CP groups, 9 RCTs [30–33, 36, 37, 39, 40, 42] with 12,884 patients were included for this meta-analysis: RR = 0.98, 95% CI: 0.89–1.07, p = 0.62; heterogeneity χ^2 = 9.99, df = 8, p = 0.27, I^2 = 20%. For IVIG, 3 RCTs [26, 27, 29] with 167 patients were included: RR = 0.96, 95% CI: 0.56–1.64, p = 0.88; heterogeneity χ^2 = 3.50, df = 2, p = 0.17, I^2 = 43%.

Adverse Events

Eleven RCTs [27–35, 41, 42] (3 IVIG and 8 CP) were performed safety meta-analysis. It showed that no significant differences between the intervention group and the control group in the number of patients with reported adverse events (Fig. 6, RR 1.07, 95% CI: 0.94–1.22, p = 0.28; heterogeneity χ^2 = 8.91, df = 7, p = 0.26, I^2 = 21%). For IVIG, 3 RCTs [27–29] with 183 patients were available in terms of reported adverse events (Fig. 6): RR 1.13,

95% CI: 0.75–1.70, p = 0.56; heterogeneity χ^2 = 0.37, df = 1, p = 0.54, I^2 = 0%. And there was no difference in reported adverse events between CP and placebo for COVID-19 patients (Fig. 6): RR 1.07, 95% CI: 0.93–1.22, p = 0.35; heterogeneity χ^2 = 8.53, df = 5, p = 0.13, I^2 = 41%.

Discussion

This is a high-quality comprehensive meta-analysis to evaluate the efficacy and safety of IVIG and CP therapy for COVID-19. In order to ensure the credibility of the meta-analysis, all nonrandomized controlled trials such as cohort studies were excluded [43, 44]. Similarly, preprints that have not been peer-reviewed were not included [45, 46].

Compared with placebo in combination with standard of care or only standard of care, treatment with IVIG was significantly associated with a decrease in all-cause mortality among patients with COVID-19 in this meta-analysis. A multicenter retrospective study in China showed that the use of high-dose IVIG could significantly reduce the mortality of severe patients with COVID-19 [17]. However, the outcomes of our analysis did not support this result because we found that the effect of IVIG on reducing the mortality of COVID-19 patients was not positively correlated with its dose. The use of high-dose (0.4 g/kg/day) IVIG did not significantly reduce the number of deaths in Tabarsi et al. [26]. Time of initiation of IVIG may be a key factor for efficacy in the treatment of
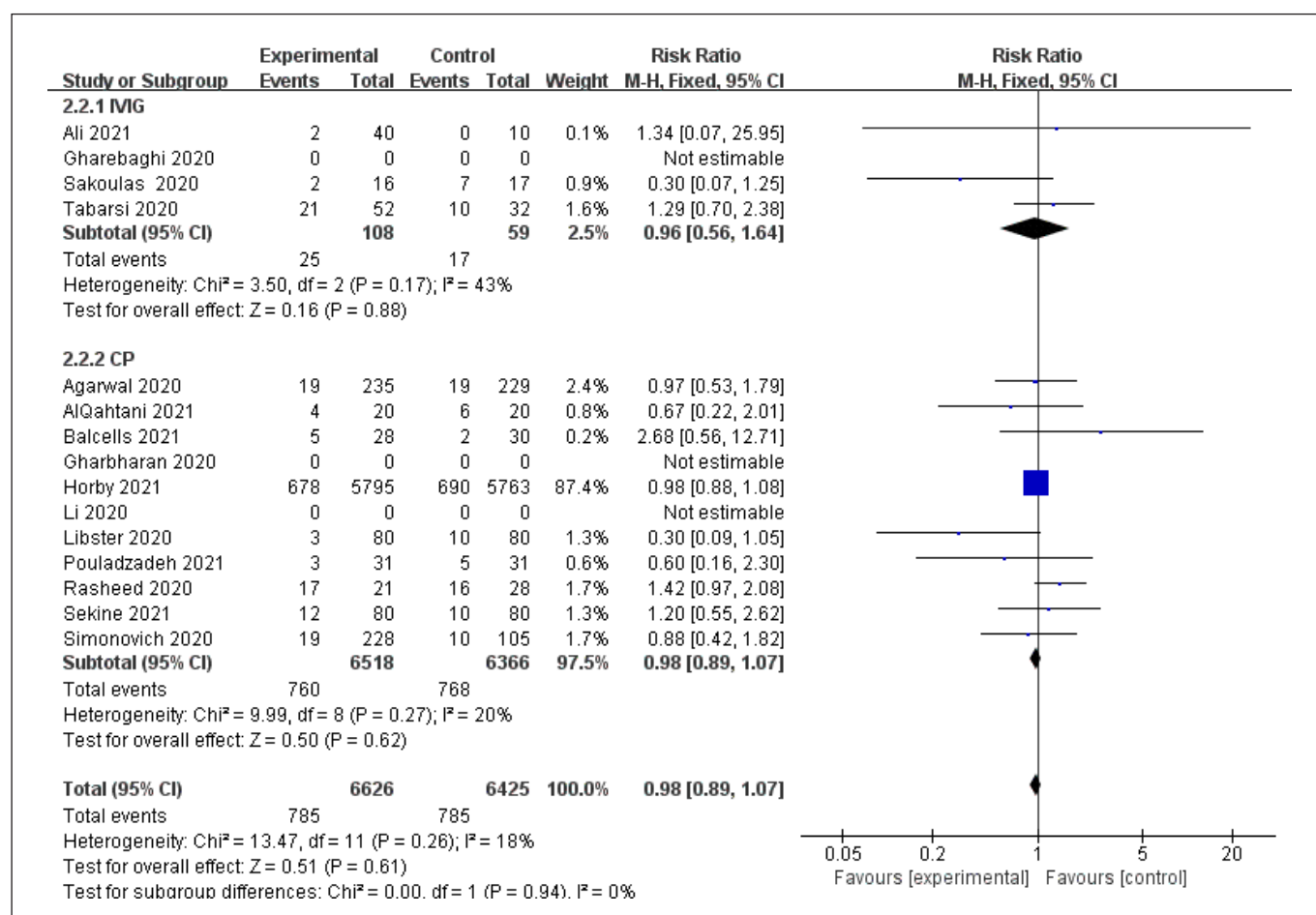
Fig. 5. Forest plots of mechanical ventilation use (12 comparisons, *n* = 13,051).

COVID-19. Treatment with IVIG within 48 h of admission not only reduced 28-day mortality (23.3% vs. 57.1%, *p* = 0.009) but also shortened hospital length of stay in a retrospective study that included 58 COVID-19 patients in Wuhan in 2020 [47]. Similarly, the early use of IVIG was superior to the placebo group in terms of reducing mortality in Gharebaghi et al. [25]. It has been demonstrated that IVIG can inhibit complement function and downregulates T-cell function, which may prevent the production of a large number of proinflammatory cytokines and chemokines and the subsequent development of cytokine storm in the early stage of the disease [48, 49]. Besides, there were significant differences in antibody content of IVIG from different manufacturers and even different batches because IVIG was prepared from pooled plasma of healthy people [48]. The production of hyperimmune anti-SARS-CoV-2 IVIG (C-IVIG) from pooled COVID-19 CP increased the chance of survival and reduced the risk of disease progression in severe and critical COVID-19 patients in Ali et al. [29]. Therefore, it is meaningful to analyze and optimize the nature or level of antibodies in IVIG to target customized patients in fur-

ther studies. Theoretically, if IVIG poses a positive impact, the length of the hospital stay, or mechanical ventilation use will be shortened because the patients will be discharged earlier in the intervention group [27]. But the use of IVIG was not associated with a low length of hospital stay and mechanical ventilation use in this meta-analysis. The longer duration of hospitalization or mechanical ventilation may be due to the higher survival rate in the IVIG group for some patients [26]. In spite of it all, there were numerous factors to affect the results such as time of initiation, daily dose, duration of the IVIG administration, function of standard of care, and so on. Hence, the results should be interpreted with great caution.

The difference in all patient-related clinical outcomes between CP and the controlled group did not meet statistical significance. It meant no significant association of CP with benefits on reduction in mortality, length of hospital stay, or mechanical ventilation use. A systematic review published in 2021 summarized evidence from 2 RCTs and 5 cohort studies addressing CP (*n* = 5,444 patients) conducted during the COVID-19 pandemic and suggested that the use of CP did not reduce the mortality of COVID-19
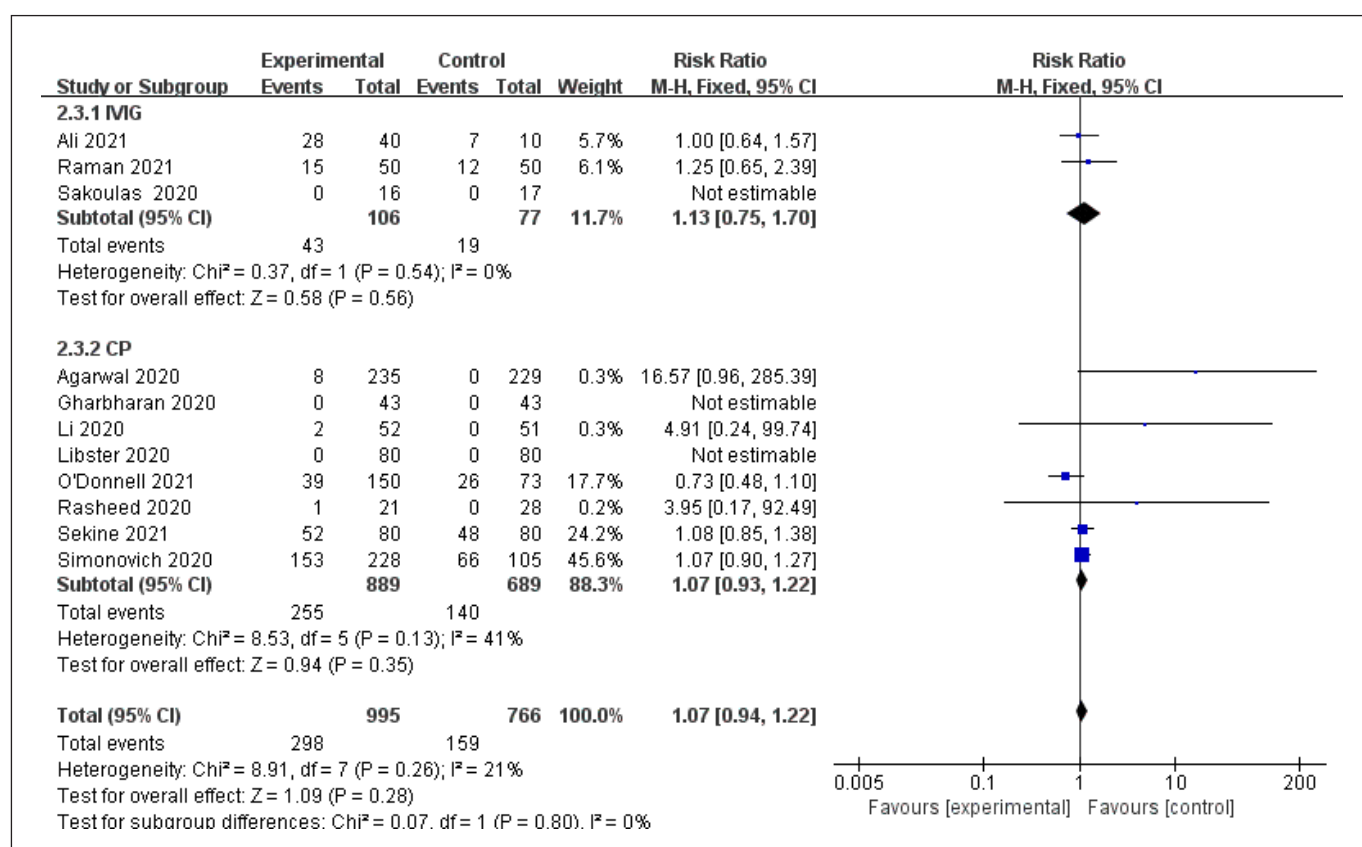
Fig. 6. Forest plots of adverse events (11 comparisons, $n = 1,761$).

patients (OR 0.44, 95% CI: 0.25–0.77) and improve clinical outcomes [50]. The results were consistent with the finding of this meta-analysis. In addition to the clinical outcomes assessed in this meta-analysis, other outcomes were performed in included RCTs such as the effect of CP on viral load. Because there were inconsistencies in the definitions used and insufficient reporting of relevant details in RCTs [26, 34, 40], we did not make a summary and analysis in this study although the decrease in viral load may be a predictor of improvement. There was a view that donor selection with different antibody titers and timing of CP treatment maymight affect the clinical efficacy for COVID-19 [34]. But it has been demonstrated that high-titer CP did not improve survival and other clinical outcomes regardless of the timing of CP treatment for patients in the latest largest RCT that involved 11,558 patients in the UK published in *The Lancet* [36].

Neutralizing antibody levels in COVID-19 patients maymight be detected after 2 weeks after symptom onset [51]. By the time these antibodies developed in patients with severe disease, significant lung injury, sepsis, and coagulation dysfunction may have already occurred [52]. Early introduction of neutralizing antibodies to COVID-19 patients could neutralize the virus' infectivity directly and bring clinical benefit to the patient through antibody-mediated pathways like complement activation and ADCC. Libister et al. [33] suggested early administration of high-titer CP against SARS-CoV-2 to mildly ill-infected patients reduced the progression of COVID-19 to severe illness. However, the result was not found in Agarwal et al. [31]. It maymight be attributed to the difference in the patient selection in that the patients included were older in Libister et al. [33]. Given the differences in the timing of CP treatment in multiple RCTs, the association between the timing of treatment and efficacy should be cautiously considered. The benefit of early use of CP may be limited by various factors, including the age and severity of the patients, the production of antibodies, and so on. Rasheed et al. [32] showed the patients who haved already started producing SARS-CoV-2 IgG and IgM arewere more likely to benefit from CP, but subgroup analysis was not performed due to the limited data. How to find the best time point for earlier CP treatment and limit the use of CP to the optimal patients is important and meaningful in future studies.It is important and meaningful for earlier CP treatment to find the best time point and limit the use of CP to the optimal patients in future studies.

For safety, there was no significant difference between IVIG or CP and placebo in combination with standard of

care or only standard of care in reported adverse events. Most of the included RCTs only reported 0 adverse events. Hence, IVIG and CP are safe treatments for COVID-19.

As mentioned above, IVIG is derived from the plasma of healthy donors, and it is a valuable resource. CP is just derived from persons who have recovered from SARS-CoV-2 infection. It is difficult for them to meet the huge demand during the pandemic. In addition, plasma, unlike other drugs, requires strict management of its collection, screening, and infusion. Finally, the titers of antibodies in the plasma must reach a certain level to work, while the level of antibodies of different donors varies greatly. All these limit the application of blood derivative in clinical treatment. The world is suffering from the second round of the impact of the COVID-19 epidemic, that is, the rampant spread of SARS-CoV-2 variants [53]. So, the search for a clinically effective treatment is still a major concern globally. Blood derivative therapy is a potential treatment, although it still has many challenges to be solved. At present, we need to pay attention not only to how to solve the problem of the limited source of plasma but also to achieve the best effect of blood derivative therapy. Dozens of clinical trials that assess the treatment with IVIG and CP have been registered in the ClinicalTrials.gov platform and other platforms, so additional evidence in the future may change the direction of the analyses in this review.

Limitations

This study has several limitations that may affect the results of our meta-analysis. Although the search strategy is strict, certain studies are not included such as non-English or non-Chinese and the publications that are not in the searched database. Six of the 18 RCTs had a high risk of bias, although those 6 RCTs only contributed to 3.4% of the weight of the meta-analysis on all-cause mortality. In addition, except for 6 RCTs with moderate patients, all patients were hospitalized with severe to critical COVID-19. The generalizability of the results to patients with milder COVID-19 is unclear. And as a secondary analysis, we have to convert some data that are not primitive such as the length of hospital stay. Finally, the number of clinical trials about CP and IVIG is limited so far.

Conclusions

Treatment with IVIG is a safe and effective treatment to improve survival for patients with COVID-19, but its effect on other clinical outcomes is uncertain. The use of CP compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality orany benefit for other clinical outcomes. The certainty of the evidence was moderate for all outcomes. It may be a key to explore the appropriate recipient of CP and time of initiation of IVIG for the treatment of COVID-19 in further study. And C-IVIG, a promising therapy for COVID-19, needs to be verified by more sophisticated RCT.

Statement of Ethics

The systematic review did not require any Ethics Committee approval. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results.

Conflict of Interest Statement

The authors do not have any conflicts of interest to declare.

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Author Contributions

Z.F., X.D., Z.C., H.C., and C.L. were involved in review conception and design. Z.F. and H.C. developed the review protocol. Z.F., X.D., and Z.C. performed searches, identified publications to include in the review, and synthesised results. Z.F. wrote the first draft of the review. H.C. critically revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary files. Further inquiries can be directed to the corresponding author.

References

1 World Health Organization (WHO). WHO Corona virus (COVID-19) dashboard. 2021 [updated 2021 Aug 3]. Available from: https://www.who.int/ (accessed August 3, 2021).

2 Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med. 2020; 382(18):1708–20.

3 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.

4 Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15.

5 Hodgson SH, Mansatta K, Mallett G, Harris V, Emary KRW, Pollard AJ. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2. Lancet Infect Dis. 2021;21(2):e26-35.

6 Nainu F, Abidin RS, Bahar MA, Frediansyah A, Emran TB, Rabaan AA, et al. SARS-CoV-2 reinfection and implications for vaccine development. Hum Vaccin Immunother. 2020;16(12):3061–73.

7 Leung K, Shum MH, Leung GM, Lam TT, Wu JT. Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. Euro Surveill. 2021;26(1):2002106.

8 Mwenda M, Saasa N, Sinyange N, Busby G, Chipimo PJ, Hendry J, et al. Detection of B.1.351 SARS-CoV-2 variant strain: Zambia, December 2020. MMWR Morb Mortal Wkly Rep. 2021;70(8):280–2.

9 Francisco RDS Jr, Benites LF, Lamarca AP, de Almeida LGP, Hansen AW, Gularte JS, et al. Pervasive transmission of E484K and emergence of VUI-NP13L with evidence of SARS-CoV-2 co-infection events by two different lineages in Rio Grande do Sul, Brazil. Virus Res. 2021;296:198345.

10 Hoffmann M, Arora P, Groß R, Seidel A, Hörnich BF, Hahn AS, et al. SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies. Cell. 2021;184(9):2384–93.e12.

11 Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature. 2021;593(7857):130–5.

12 Cele S, Gazy I, Jackson L, Hwa SH, Tegally H, Lustig G, et al. Escape of SARS-CoV-2 501Y.V2 from neutralization by convalescent plasma. Nature. 2021;593(7857):142–6.

13 Mallapaty S. India's massive COVID surge puzzles scientists. Nature. 2021;592(7856):667–8.

14 Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787–99.

15 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–43.

16 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475–81.

17 Cao W, Liu X, Hong K, Ma Z, Zhang Y, Lin L, et al. High-dose intravenous immunoglobulin in severe Coronavirus disease 2019: a multicenter retrospective study in China. Front Immunol. 2021;12:627844.

18 Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24(1):44–6.

19 Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, et al. Feasibility of using convalescent plasma immunotherapy for MERS-CoV infection, Saudi Arabia. Emerg Infect Dis. 2016;22(9):1554–61.

20 van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med. 2016;374(1):33–42.

21 Huang S, Shen C, Xia C, Huang X, Fu Y, Tian L. A retrospective study on the effects of convalescent plasma therapy in 24 patients diagnosed with COVID-19 pneumonia in February and March 2020 at 2 centers in Wuhan, China. Med Sci Monit. 2020;26:e928755.

22 Pei L, Zhang S, Huang L, Geng X, Ma L, Jiang W, et al. Antiviral agents, glucocorticoids, antibiotics, and intravenous immunoglobulin in 1142 patients with coronavirus disease 2019: a systematic review and meta-analysis. Pol Arch Intern Med. 2020;130(9):726–33.

23 Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. CMAJ. 2020;192(27):E745-55.

24 Wenjing L, Yuanzhen F, Li JY, Tang LV, Yu H. Safety and efficacy of convalescent plasma therapy in severely and critically ill patients with COVID-19: a systematic review with meta-analysis. Aging. 2020;13(1):1498–509.

25 Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi SR, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis. 2020;20(1):786.

26 Tabarsi P, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, et al. Evaluating the effects of intravenous immunoglobulin (IVIg) on the management of severe COVID-19 cases: a randomized controlled trial. Int Immunopharmacol. 2021;90:107205.

27 Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in Coronavirus disease 2019. Crit Care Explor. 2020;2(11):e0280.

28 Raman RS, Bhagwan Barge V, Anil Kumar D, Dandu H, Rakesh Kartha R, Bafna V, et al. A phase II safety and efficacy study on prognosis of moderate pneumonia in Coronavirus disease 2019 patients with regular intravenous immunoglobulin therapy. J Infect Dis. 2021;223(9):1538–43.

29 Ali S, Uddin SM, Shalim E, Sayeed MA, Anjum F, Saleem F, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: a phase I/II randomized control trial. EClinicalMedicine. 2021;36:100926.

30 Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vázquez C, et al. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. N Engl J Med. 2021;384(7):619–29.

31 Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ. 2020;371:m3939.

32 Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill covid-19 patients residing in respiratory care units in hospitals in baghdad, Iraq. Infez Med. 2020;28(3):357–66.

33 Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe COVID-19 in older adults. N Engl J Med. 2021;384(7):610–8.

34 Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA. 2020;324(5):460–70.

35 Gharbharan A, Jordans CCE, GeurtsvanKessel C, den Hollander JG, Karim F, Mollema FPN, et al. Effects of potent neutralizing antibodies from convalescent plasma in patients hospitalized for severe SARS-CoV-2 infection. Nat Commun. 2021;12(1):3189.

36 Horby PW, Estcourt L, Peto L, RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2020;396(10259):1345–52.

37 AlQahtani M, Abdulrahman A, Almadani A, Alali SY, Al Zamrooni AM, Hejab AH, et al. Randomized controlled trial of convalescent plasma therapy against standard therapy in patients with severe COVID-19 disease. Sci Rep. 2021;11(1):9927.

38 Bennett-Guerrero E, Romeiser JL, Talbot LR, Ahmed T, Mamone LJ, Singh SM, et al. Severe acute respiratory syndrome Coronavirus 2 convalescent plasma versus standard plasma in Coronavirus disease 2019 infected hospitalized patients in New York: a double-blind randomized trial. Crit Care Med. 2021;49(7):1015–25.

39 Pouladzadeh M, Safdarian M, Eshghi P, Abolghasemi H, Bavani AG, Sheibani B, et al. A randomized clinical trial evaluating the immunomodulatory effect of convalescent plasma on COVID-19-related cytokine storm. Intern Emerg Med. 2021;16(8):2181–91.

40 Balcells ME, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos ME, Ferrés M, et al. Early versus deferred anti-SARS-CoV-2 convalescent plasma in patients admitted for COVID-19: a randomized phase II clinical trial. PLoS Med. 2021;18(3):e1003415.

41 O'Donnell MR, Grinsztejn B, Cummings MJ, Justman JE, Lamb MR, Eckhardt CM, et al. A randomized double-blind controlled trial of convalescent plasma in adults with severe COVID-19. J Clin Invest. 2021;131(13):e150646.

42 Sekine L, Arns B, Fabro BR, Cipolatt MM, Machado RRG, Durigon EL, et al. Convalescent plasma for COVID-19 in hospitalised patients: an open-label, randomised clinical trial. Eur Respir J. 2022 Feb 10;59(2):2101471.

43 Abolghasemi H, Eshghi P, Cheraghali AM, Imani Fooladi AA, Bolouki Moghaddam F, Imanizadeh S, et al. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: results of a multicenter clinical study. Transfus Apher Sci. 2020;59(5):102875.

44 Khamis F, Al-Zakwani I, Al Hashmi S, Al Dowaiki S, Al Bahrani M, Pandak N, et al. Therapeutic plasma exchange in adults with severe COVID-19 infection. Int J Infect Dis. 2020;99:214–8.

45 Bajpai M, Kumar S, Maheshwari A, Chhabra K, kale P, Gupta A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. medRxiv [Preprint]. 2020.

46 Gonzalez JLB, Gámez MG, Enciso EAM, Maldonado RJE, Palacios DH, Campos SD, et al. Efficacy and safety of convalescent plasma and intravenous immunoglobulin in critically ill COVID-19 patients. a controlled clinical trial. medRxiv [Preprint]. 2021.

47 Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, et al. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020;81(2):318–56.

48 Zandman-Goddard G, Shoenfeld Y. Autoimmunity: from bench to bedside [Internet]. El Rosario University Press; 2013.

49 Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39(7):2085–94.

50 Sarkar S, Soni KD, Khanna P. Convalescent plasma is a clutch at straws in COVID-19 management! A systematic review and meta-analysis. J Med Virol. 2021;93(2):1111–8.

51 Wang X, Guo X, Xin Q, Pan Y, Hu Y, Li J, et al. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients. Clin Infect Dis. 2020; 71(10):2688–94.

52 Okba NM, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. Emerg Infect Dis. 2020; 26(7):1478–88.

53 Dyer O. COVID-19: delta infections threaten herd immunity vaccine strategy. BMJ. 2021; 374:n1933.